REMARKS

Independent claims 22 and 30 have been amended. Support for the amendment appears in the "Summary of the Invention" on page 3 of the application as originally filed. Entry of the amendment is respectfully requested. Furthermore, the amendment is consistent with the showing set forth in the attached Declaration.

The undersigned would like to thank Examiner Lamm for the courtesy extended by her in consenting to an interview on April 19, 2006 so that the pending Office Action and experimental evidence in support of patentability set forth in the attached Declaration under 35 U.S.C. §1.132 could be presented and discussed in person. At the interview, the undersigned expressed the belief that the experimental evidence was particularly surprising and that consideration of the Declaration in combination with a detailed response to the Office Action would expedite prosecution and allowance of the claims. The Examiner was also apprised of the intention to amend the claims to include a reference to permeability.

To briefly review, the invention is directed to a tablet comprising an active ingredient wherein the tablet composition effectively increases absorption of the active ingredient across the oral mucosa, including buccal, sublingual and gingival surfaces. The application teaches that this can be achieved by, for example, combining an active ingredient with an effervescent couple and a pH adjusting substance, all of which are released in the oral cavity. The claims previously have been amended in order to streamline prosecution, such that the pending claims are specifically directed to fentanyl or its pharmaceutically acceptable salt as the active ingredient and the pH adjusting substance is a basic material.

In the Office Action mailed October 19, 2005, claims 22, 23, 25-27, 30-33, 36, 83, 84, 86, 88, 91, 93, and 94 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,200,604. In response to this provisional rejection, Applicants submit a Terminal Disclaimer in suitable form thereby obviating this rejection. Entry of the Terminal Disclaimer and withdrawal of this aspect of the rejection is respectfully requested.

Furthermore, claims 22, 23, 25-27, 30-33, 36, 83, 84, 86, 88, 91, 93, and 94 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 10-15 and 17-19 of copending Application No. 10/080,016 (now U.S. 6,974,590, issued Dec. 13, 2005, and it has also been included in the terminal disclaimer); claims 1-30 of copending Application No. 11/026,132; claims 1-30 of copending Application No. 11/027,353; claims 1-22 of copending Application No. 11/026,327; and claims 1-5, 7-10 and 12-17 of copending Application No. 10/977,029. If, as expected, the claims of the present application are allowed in response to the present submissions, a terminal disclaimer over the claims of the pending applications is not required.

Applicants rely in part on the enclosed Declaration under 37 C.F.R §1.132, which is being submitted in support of patentability and which includes definitive experimental evidence clearly demonstrating that the combined effect of an effervescent couple and pH adjusting substance on the permeability of fentanyl across a mucosal membrane is so significant and unexpected (an increase of several hundred percent!) that such effect cannot be considered an obvious combination of elements from disparate sources.

To demonstrate their advance, Applicants conducted controlled experiments, the results of which are set forth in the accompanying Declaration of Dr. Vikas Agarwal, Group Leader, Formulation Development for the assignee of the application, CIMA LABS Inc. As can be observed, three compositions were tested: the first included both an effervescent couple and a pH adjusting substance to adjust the pH to a basic level. The second composition, not within the scope of the claims, contained only an effervescent couple (no pH adjusting substance) and the third, also not within the scope of the claims, only a pH adjusting substance (no effervescent couple). The concentrations of these functional components were adjusted and maintained equal in each of the test compositions. A standard *in vitro* test method described in detail in the Declaration was used to measure permeability of fentanyl across a mucosal membrane.

The test results were extraordinary. Fentanyl permeability across the oral mucosa from the composition containing both an effervescent couple and pH adjusting substance was more than 410% greater than that for the composition containing only an effervescent couple and more than 510% greater than a composition containing only a pH adjusting substance. It is respectfully submitted that these experiments confirm that there is nothing in the art to suggest that combining both an effervescent couple and a pH adjusting substance in a single composition could cause a significant increase in the permeability of fentanyl across a mucosal membrane. Thus, if the Patent Office had established a *prima facie* case of obviousness, which is not the case, it would have been completely rebutted by this showing. Accordingly, withdrawal of the claim rejections is therefore respectfully requested.

Turning to the rejections of the claims under 35 U.S.C. §103(a) and the cited references, claims 22, 23, 26, 27, 30-33, 36, 83, 84, 86, 88, 91, 93, and 94 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over *McCarty*, U.S. 5,073,374 (hereinafter "*McCarty*") in view of *Wehling et al.*, WO 91/04757 (hereinafter "*Wehling*") and further in view of *Streisand* et al. ("Buccal absorption of fentanyl is pH-dependent in dogs," Anesthesiology, (1995 Mar), 82 (3), pp. 759-64; hereinafter "*Streisand*"). Applicants respectfully traverse. It is respectfully submitted that the rejection is nothing more than a hindsight reconstruction of the claimed invention.

McCarty teaches fast dissolving tablets for buccal administration of an active ingredient and included among the list of such active materials is fentanyl. Fentanyl is not exemplified. The Office acknowledges that *McCarty* does not teach the use of an effervescent couple and furthermore, neither does it teach the use of a pH adjusting substance.

To cure the deficiencies of *McCarty*, the Office cites *Wehling* for its teaching of effervescent dosage forms for direct oral administration. The problems solved by *Wehling* is that of taste masking drugs having objectionable taste, facilitating disintegration, and providing a pleasing organoleptic sensation. The Office asserts that the motivation to combine *McCarty* and *Wehling* is found in the desire "to obtain even faster dissolution as well as masking objectionable flavor of medicaments and providing pleasant organoleptic sensation." However, such a combination cannot be made in view of the fact that *Wehling* requires that the active ingredient be present as coated microparticles that are to pass quickly out of the mouth and into the digestive system. (See p. 9, lns. 10-17).

The coating of *Wehling* is essential for taste masking because it prevents the drug from dissolving in the mouth. Yet *McCarty* requires rapid dissolution. Thus the combination would prevent, rather than enhance dissolution. Moreover, *Wehling* is directed to a tablet that disintegrates in the mouth. It neither teaches not suggests that the use of an effervescent couple could enhance trans-mucosal absorption. Finally, the use in *McCarty* of the effervescent couple of *Wehling* requires abandoning the essence of the *McCarty* invention - tablet disintegration *via* a high concentration of a fast dissolving sugar. There's nothing to suggest that tablet disintegration in *Wehling* is faster than that in *McCarty* or that an effervescent couple would enhance disintegration speed. Nor is there anything in either reference to teach or suggest the use of an effervescent couple in an amount which is greater than the amount necessary for tablet disintegration and which is sufficient to increase absorption across the oral mucosa.

Thus even though *Wehling* is not directed to transfer of an active ingredient across the oral mucosa, and indeed would actively work against such delivery, its teachings have been selectively gleaned *via* hindsight reconstruction in order to adopt only individual features that relate to the present invention in order to combine with *McCarty*, while disregarding essential teachings, necessary limitations and the actual inventions of both *McCarty* and *Wehling*.

The Office further acknowledges that *Wehling* doesn't explicitly teach the use of a pH adjusting substance (and neither does *McCarty*), but that this failing can be cured by *Streisand*, which is said to teach that "buccal absorption, bioavailability and permeability of fentanyl are pH dependent and increase as the pH of the fentanyl solution becomes more basic." (Action, p. 8) The Office concludes that "it would have

been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to modify the teaching of *Wehling* et al. such as to employ the excess of the carbonate source (base)" as suggested by *Streisand*.

Such reasoning is contrary to *Streisand* and is again the product of hindsight. Specifically, *Streisand* is directed to increasing the delivery of a drug substance by causing a change in the form of the drug (e.g., ionized to unionized) as a consequence of modifying pH. However, according to *Streisand* in order to observe the effect of altered pH it is necessary to obtain a true solution of fentanyl, compared to conditions wherein the active ingredient may or may not achieve a true solution in the region adjacent to the oral mucosa (p. 4, col. 1). However, neither a true solution nor a modified drug form can be achieved in an oral cavity according *Wehling* since the active medicament must be covered with a protective coating to prevent exposure and the resulting coated particles are swallowed. Consequently, one skilled in the art would not look to *Streisand* to modify *Wehling* for delivery of an active medicament in the oral cavity because *Wehling* requires that such a condition is to be avoided.

Streisand merely confirms the Henderson-Hasselbach (H-H) effect that's disclosed in the present application (starting at p.5, ln. 27), and provides an invitation to conduct further experiments. The *Streisand* authors also question the practical significance of their work, "Can the results of our study be related to clinical practice?" (p. 5, last col.) In other words, there's nothing in *Streisand* to suggest that the results can be translated into a practical effect and certainly there's nothing to suggest combining its teachings with the use of an effervescent couple as taught by the present invention.

In conclusion, the combination of selective features of these disparate references requires ignoring the nature of the inventions in the patents (*McCarty* and *Wehling*) and extrapolation of the third, *Streisand*, beyond what it necessarily and reasonably teaches. And the only real motivation to take these extreme steps is the selective, hindsight reconstruction of Applicants' invention. Withdrawal of this aspect of the rejection is respectfully requested.

Claims 22, 23, 25-27, 30-33, 36, 83, 84, 86, 88, 91, 93, and 94 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over *Chen et al.* ("Studies on formulations of fentanyl buccal adhesive tablets," Zhongguo Yiyao Gongye Zazhi, 1997, 28 (3), 129-131 (Abstract only, hereinafter "*Chen*") in view of *Wehling* and further in view of *Streisand*. This rejection is respectfully traversed.

The Office relies on *Chen* for its teaching relating to the use of a bioadhesive fentanyl tablet. It does not teach the use of an effervescent couple or the use of a pH adjusting substance. Contrary to the suggestion by the Office that one skilled in the art would have been motivated to modify *Chen* to employ effervescent tablets based on *Wehling* in order to mask the taste of the fentanyl, it is observed that the methods and objectives of *Chen* and *Wehling* are in opposition. *Wehling* seeks to rapidly disintegrate a tablet containing protected microparticles for rapid removal from the mouth (swallowing) and *Chen* seeks to maintain the drug composition in the buccal region of the mouth using a bioadhesive. Further, as discussed above, the limited teaching of *Streisand* is insufficient to provide a significant improvement.

Finally, none of the references provide any teaching or suggestion that if an effervescent couple is employed, the

amount should exceed that needed merely for tablet disintegration so as to increase transfer of a drug across the oral mucosa. And in particular, none of the references, individually or in combination, suggest combining an effervescent couple with a pH adjusting substance in the reasonable expectation of significantly improving transmucosal permeability. The attention of the Office is once again invited to consider the accompanying Declaration, as discussed above. Withdrawal of this aspect of the rejection is respectfully requested.

As it is believed that all of the rejections set forth in the Official Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that she telephone Applicants' attorney at (908) 654-5000 in order to overcome any additional objections that she might have.

If there are any additional charges in connection with this requested amendment, the examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: April 19, 2006

Respectfully submitted,

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Docket No.: CIMA 3.0-030 CONT CONT
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Wang et al.

Application No.: 09/661,693 Examiner: M. Lamm

Filed: September 14, 2000 Art Unit: 1616

For: SUBLINGUAL BUCCAL EFFERVESCENT

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Vikas Agarwal hereby declare as follows:

1. That I am Group Leader for Formulation Development at CIMA LABS Inc. (a Cephalon Company) and I have been employed by CIMA since February, 2001. That I have a Bachelor of Science from Birla Institute of Technology and Science, Pilani, India and a Ph.D. in the field of Pharmaceutical Sciences from Texas Tech University, Health Sciences Center, Amarillo, Texas conferred in 2001.

2. That my responsibilities include management, research, development and improvement of pharmaceutical delivery forms, including that which is the subject of the above-identified patent application.

3. That as part of CIMA's efforts to confirm the performance and active drug delivery characteristics of solid dosage forms containing fentanyl, I commissioned a study by

Absorption Systems, based in Exton, PA that conducts contract research for the pharmaceutical industry with a focus on ADME (an acronym for Absorption, Distribution, Metabolization, and Excretion).

4. That the study was designed to compare the mucosal permeability characteristics of tablet dosage forms according to the formulations shown in Table I attached, utilizing, in various combinations, an effervescent couple, a pH adjusting substance and the active ingredient fentanyl citrate, plus the identified, common pharmaceutical excipients.

5. That specifically, the observed data compared composition 1, containing both an effervescent couple and a pH adjusting substance with a similar composition, which contained an effervescent couple and no pH adjusting substance (designated composition 2), and a composition which contained a pH adjusting substance and no effervescent couple (designated composition 3). As noted, in each instance fentanyl was the active ingredient.

6. That the amounts of inert excipient or filler in compositions 2 and 3 were increased so that the concentration of the pH adjusting substance and effervescent couple would be at the same levels as in composition 1.

7. That an *in vitro* test method known to those skilled in the art prior to the filing date of the present application was used to evaluate permeability of the active agent, fentanyl, as described in detail in the attachment. The method utilizes cultured buccal cells, as discussed in K.L. Audus et al., "The Use of Cultured Epithelial and Endothelial Cells for Drug Transport and Metabolism Studies," Pharm. Res., 7, 5, 435-451 (1990).

8. That, the permeability data shown in the table and illustrated in the attached figure clearly demonstrate that the claimed composition results in significantly superior performance compared to compositions in which only an effervescent couple or only a pH adjusting substance is present. Specifically, the permeability value obtained using formula 1 is more than 410% greater than that of formula 2 (effervescent couple only), and more than 511% greater than that of formula 3 (pH adjusting substance only).

9. That I conclude that these data confirm that a composition including both an effervescent couple and a basic pH adjusting substance results in significantly enhanced permeability of fentanyl across a mucosal membrane.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statements may jeopardize the validity of this application or any patent issuing therefrom.

Signed this 18th day of April, 2006

Vikas Agarwal

Table
Test Compositions (wt%)

Component	Function	1 Effervescence + pH	2 Effervescence Only	3 pH Only
Fentanyl Citrate	Active	0.628	0.628	0.628
Mannitol	Filler	47.872	57.872	83.872
Disintegrant	Disintegrant	3.000	3.000	3.000
Sodium Bicarbonate	Effervescent component	21.000	21.000	-
Citric Acid	Effervescent Component	15.000	15.00	-
Sodium Carbonate	pH Adjusting Substance	10.000	-	10.000
Magnesium Stearate	Lubricant	2.000	2.000	2.000
Pigment	Color	0.500	0.500	0.500
Test Results Mean (std. deviation)				
Fentanyl Permeability, P_{app} (x 10^{-6} cm/sec)		95.6 (3.1)	23.3 (4.1)	18.7 (2.6)

Determination of Average Apparent Permeability (*In vitro* Test Method)

Experimental Procedure

Materials

Krebs Ringer Bicarbonate (KRB) buffer was obtained from Sigma-Aldrich (St. Louis, MO). HEPES zwitterionic buffer solution was purchased from Invitrogen (Grand Island, NY). The reservoir buffer consisted of filtered KRB buffer containing 10 mM HEPES and 0.015 mM sodium bicarbonate at pH 7.0. Tablets according to the formulations shown in the above table were prepared by direct compression using a standard rotary press. Tablet weight for each of the tablets was 200 mg, corresponding to a 5/16 inch (0.794 cm)

size. EpiOral® cells used for the permeability tests are described below.

Permeation Study through EpiOral Cell Line

EpiOral® cells plated in 6 well plates and accompanying buffer solutions for donor and receiver chambers were obtained from MatTek Corporation (Ashland, MA; a detailed product description is available at www.mattek.com). The permeation experiment was done according to instructions from the manufacturer on the second day of cell arrival. Donor buffer consisted of Dulbeccos' Phosphate Buffered Saline (DPBS) without Ca and Mg chloride, pH 7.0. The receiver buffer consisted of Dulbeccos' Phosphate Buffered Saline without Ca and Mg Chloride, pH 7.4, with 1 % BSA added to improve fentanyl recovery from the apparatus.

The receiver chamber was filled with 1 mL buffer while the donor chamber was filled with 2 mL buffer. The donor buffer was applied in 0.5 mL increments/1 min for a total volume of 2 mL. At time zero, 50 µL of the donor solution was sampled. At the end of the experiment, the complete donor content was collected at 150 minutes (or 120 minutes in experiments on the second batch of cells). Receiver samples (200 µL) were collected at 0, 30, 60, 90, 120 and 150 minutes and replaced with an equal volume of fresh receiver buffer (or at 0, 15, 30, 60, 90 and 120 minutes on second batch of cells). Fentanyl permeation was tested by application of the tablet formulations. Tests were run in triplicate.

Sample Analysis

Fentanyl was measured by LC/MS/MS using electrospray ionization.

Data Analysis

Cumulative concentrations in the receiver chamber were calculated, compensating for the removal and replacement of the 0.2 mL (200 µL) sample, as follows.

$$C_r = C^n + (0.2\ mL / 1.0\ mL) \times C^{n-1}$$

where,

C_r = the cumulative concentration in the receiver chamber
C^n = the measured receiver concentration at time point, n
C^{n-1} = the measured receiver concentration at the previous time point, n-1

The apparent permeability coefficient, P_{app}, was calculated as follows:

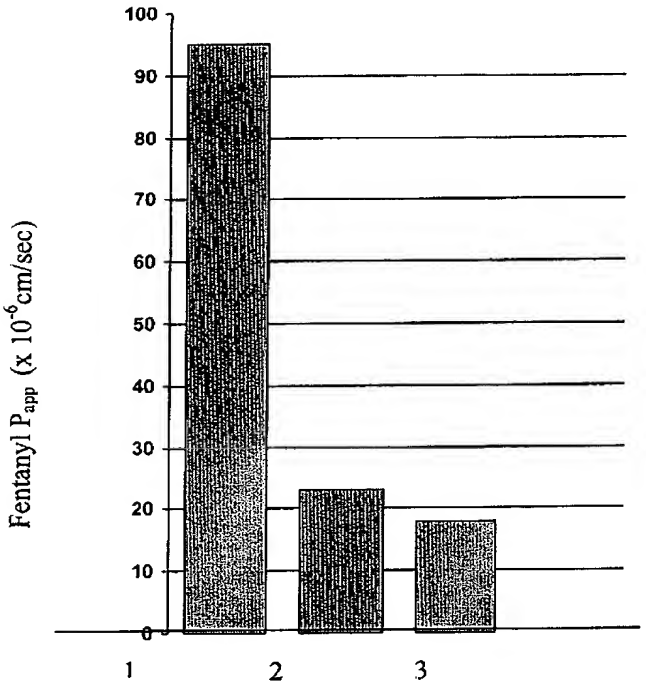
$$P_{app} = (dC_r / dt) \times V_r / (A \times C_0)$$

where,

dC_r/dt = the slope of the cumulative concentration in the receiver chamber versus time
V_r = the volume of the receiver chamber (1.0 mL)
A = the surface area of buccal epithelium available for permeation (4.2 cm^2)
C_0 = the initial concentration of compound in the donor chamber

Figure

Average apparent Permeability (P_{app}) ± STD (N=3) of Fentanyl Applied in Different Dosing Forms *In Vitro*



Treatments (Tablets)

1 - Effervescent couple + pH adjusting substance
2 - Effervescent couple only
3 - pH adjusting substance only